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(54) **Novel sulfonamide derivatives.**

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Description

TECHNICAL FIELD

This invention provides certain novel sulfonamide derivatives having analgesic and anti-irritant activity.

In general, analgesics fall into two broad categories. The simple analgesics, such as aspirin, are most effective against pain of integumental origin, headache, and muscle aches; the narcotics are more useful for deep or visceral pain. Narcotic analgesics such as morphine also produce more profound effects than simple analgesics, and are potentially addicting, with the development of tolerance and physical dependence. The narcotic analgesics appear to work through interaction with the endorphin/enkephalin system of the CNS; many of the simple, non-narcotic analgesics appear to work by inhibition of prostaglandin synthetase. The effect of narcotics is to elevate the pain threshold above the normal level; the non-narcotic analgesics act to raise an abnormally low pain threshold to the normal level. The narcotic analgesics are antagonized by N-allyl compounds such as naloxone; the non-narcotic analgesics are not.

In the field of anti-irritancy, dermal and tissue irritation can be caused by common irritants such as acids and alkalis, keratolytics and proteolytics, depilatories, plant oils, and the like. In many instances, it is observed that compounds which effectively block the action of one class of irritants are totally or substantially ineffective with other classes of irritants. The problem in the art has been compounded by the inadequacy, or unavailability in some cases, of appropriate animal models of dermal irritation. For example, most laboratory animals are insensitive to poison ivy. As a consequence, the search has long continued, in a purely empirical way, for anti-irritant compositions — not always successfully.

The present invention relates to the discovery that certain novel sulfonamide derivatives are analgesics and anti-irritants. In their analgesic action, these compounds appear to be largely unrelated to the two known classes of analgesics. In certain tests, these compounds produce a level of analgesia comparable to morphine, yet do not appear to involve the endorphin-enkephalin system, and thus should not be reversed by narcotic antagonists, such as naloxone. It is believed that these compounds will effectively prevent the development of cutaneous hyperalgesia. At high doses, it is believed that these compounds will also exert analgesic activity in classical models of deep pain, elevating the pain threshold above the normal value.

In their anti-irritant activity, these compounds are active against several irritants, including croton oil, and particularly depilatories (thioglycolates). They appear to act, not as protectants or barriers, but, rather, directly to block or eliminate responses to the irritant chemical. In addition, the sulfonamide derivatives of this invention offer the benefit of reduced discomfort on application. By contrast, compounds such as capsaicin, which possess potent anti-irritant activity, can cause irritation and reddening of the skin.

Background Art

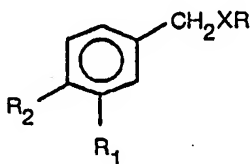
J. A. Kiernan, *Quart. J. of Exp. Physiol.*, (1977) 62, 151—161, states that capsaicin N-(3-methoxy-4-hydroxybenzyl)-8-methyl-6-nonenamide is known to confer resistance to certain chemical irritants.

Jancso, et al., *Br. J. Pharmac. Chemother.* (1967), 31, 138—151, states that by repeated administration of capsaicin, ocular and/or cutaneous pain receptors can be desensitized to chemical, but not other, stimuli.

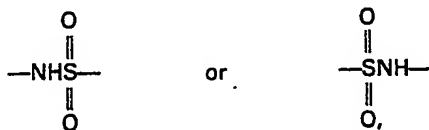
Arvier, et al., *Br. J. Pharm.* (1977), 59, 61—68, indicate that capsaicin reduces or blocks the edema formation associated with certain types of inflammation.

Disclosure of the Invention

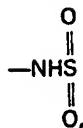
The present invention provides compounds of the following formula:



wherein X is



wherein R is C₃—C₁₂ (preferably C₆—C₁₂) alkyl or aralkyl, branched or unbranched, aryl, unsubstituted or substituted (e.g., haloaryl), or C₃—C₂₂ (preferably C₆—C₂₂) alkenyl, branched or unbranched, wherein R₁ is H, OH or OCH₃, and wherein R₂ is H or OH, at least one of R₁ and R₂ being OH or OCH₃; and pharmaceutically acceptable salts thereof. These compounds or salts thereof are hereafter generally referred to as sulfonamides. The most preferred sulfonamides are those where X is



where R_1 is OCH_3 and where R_2 is OH (the N-(3-methoxy-4-hydroxybenzyl) sulfonamides), and especially those where R is n-heptyl or n-octyl. These compounds can be made by synthesis from readily available starting materials, using standard synthetic techniques, as described hereinafter. In the practice of this invention, these sulfonamides can be administered either topically or systemically.

A. Definitions

By "safe and effective amount" is meant an amount of the sulfonamide sufficient to provide analgesic or anti-irritant activity so as to alleviate or prevent the pain or irritation being treated at a reasonable benefit/risk ratio attendant with any medical treatment. The amount of the sulfonamide used will vary with the particular condition being treated, the severity of the condition, the duration of the treatment, the specific formulation employed and the concentration of the sulfonamide therein, and like factors.

By "systemic administration" is meant introducing the sulfonamide or composition containing same into the tissues of the body, other than by topical application. Systemic administration thus includes, without limitation, oral, intrathecal, epidural, intramuscular, intravenous, intraperitoneal, and subcutaneous administration.

By "pharmaceutically acceptable" salts is meant those salts which are safe for topical or systemic administration. These include the sodium, potassium, calcium, magnesium, and ammonium salts.

By "topical application" herein is meant directly laying on or spreading the sulfonamide, or composition containing same, on epidermal or epithelial tissue (including outer skin and oral, gingival, nasal, etc. tissue).

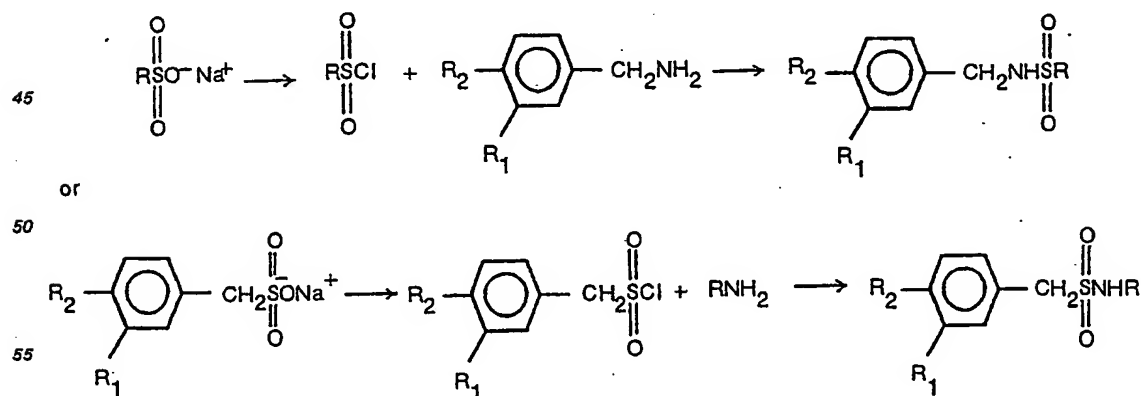
By the term "comprise" as used herein is meant that various other inert ingredients, compatible drugs and medicaments, and steps can be employed in the compositions and processes of this invention as long as the critical sulfonamides are present in the compositions and are used in the manner disclosed. The term "comprising" thus encompasses and includes the more restrictive terms "consisting essentially of" and "consisting of" which characterize the use of the essential sulfonamides in the compositions and methods disclosed herein.

By "compatible" herein is meant that the components of the composition are capable of being commingled without interacting in a manner which would substantially decrease the efficacy of the total compositions under ordinary use situations.

All percentages herein are by weight of the composition unless otherwise specified.

B. Synthesis of the Sulfonamides of the Present Invention

The sulfonamides of this invention can readily be prepared by synthesis along the lines of the following schematic and illustrative examples.



The sodium alkyl sulfonates can be prepared by the method of Reed et al., *J. Am. Chem. Soc.*, 57, p. 570 (1935).

N-(3-methoxy-4-hydroxybenzyl) octylsulfonamide was prepared by the following method:

A suspension of 10 g sodium octylsulfonate in 50 ml thionyl chloride was heated at reflux overnight. The excess thionyl chloride was removed using a rotary evaporator, and the residue was dissolved in 100 ml of diethyl ether and washed twice with water and once with brine. The ether phase was dried with

MgSO₄, filtered and evaporated to yield 5.47 g of octylsulfonyl chloride. This was dissolved in 10 ml diethyl ether and added dropwise to a suspension containing 4.87 g 3-methoxy-4-hydroxybenzylamine hydrochloride, 35 ml dimethylformamide, and 10.78 ml 5N NaOH. The resulting mixture was stirred at 28°C for 16 hrs. and then poured into a separatory funnel containing 500 ml H₂O. The aqueous mixture was extracted three times with 100 ml aliquots of diethyl ether. The ether extracts were combined and washed with 100 ml of 1N HCl, 100 ml saturated NaHCO₃, 100 ml H₂O, and 100 ml brine. The ether solution was dried over MgSO₄, filtered, and evaporated to yield a crude product containing the desired sulfonamide along with the O,N bisulfonated byproduct. The solid was triturated with ethanol and filtered; the ethanol was evaporated to recover the desired sulfonamide, which was then recrystallized from ethanol/water to yield 1.08 g of final product.

Analysis calculated for C₁₈H₂₇NO₄S: C, 58.33; H, 8.26; N, 4.25; and S, 9.73. Found: C, 58.32; H, 8.25; N, 4.07, and S, 9.95.

In a similar manner was prepared N-(3-methoxy-4-hydroxybenzyl) heptylsulfonamide; m.p. 92—93°C. Analysis calculated for C₁₅H₂₅NO₄S: C, 57.11; H, 7.98; N, 4.44; and S, 10.61. Found: C, 57.27; H, 8.14; N, 4.43; and S, 10.30.

It can be seen that preparation of the desired sulfonamides of this invention can be accomplished by selection of the appropriate sulfonate starting material, using the foregoing techniques.

C. Topical Compositions

The sulfonamides as previously described are useful when topically applied to skin. Compositions containing these compounds are also useful for topical application to skin. The compositions comprise a safe and effective amount, usually at least about 0.5%, preferably from about 1% to about 2% of the sulfonamide. The balance of the composition further comprises a pharmaceutically acceptable carrier. Suitable carriers for the sulfonamides preferably remain in place on the skin as a continuous film and resist being washed off easily by perspiration or by immersion in water. Generally, the carrier is organic in nature and capable of having dispersed or dissolved therein the sulfonamide. Lotions, creams, solutions, gels and solids are common physical forms of the compositions herein. A more detailed description of such forms follows.

1. Lotions

The lotions can comprise an effective amount of the sulfonamide; from 1% to 25%, preferably from 3% to 15%, of an emollient; the balance being water, a C₂ or C₃ alcohol, or a mixture of water and the alcohol. Several emollients are known. Examples of such emollients are as follows:

1. Hydrocarbon oils and waxes. Examples are mineral oil, petrolatum, paraffin, ceresin, ozokerite, microcrystalline wax, polyethylene, and perhydrosqualene.

2. Silicone oils, such as dimethylpolysiloxanes, methylphenylpolysiloxanes, water-soluble and alcohol-soluble silicone-glycol copolymers.

3. Triglyceride fats and oils such as those derived from vegetable, animal and marine sources. Examples include castor oil, safflower oil, cotton seed oil, corn oil, olive oil, cod liver oil, almond oil, avocado oil, palm oil, sesame oil, and soybean oil.

4. Acetoglyceride esters, such as acetylated monoglycerides.

5. Ethoxylated glycerides, such as ethoxylated glyceryl monostearate.

6. Alkyl esters of fatty acids having 10 to 20 carbon atoms. Methyl, isopropyl, and butyl esters of fatty acids are useful herein. Examples include hexyl laurate, isohexyl laurate, isohexyl palmitate, isopropyl palmitate, decyl oleate, isodecyl oleate, hexadecyl stearate, decyl stearate, isopropyl isostearate, diisopropyl adipate, diisohexyl adipate, dihexyldecyl adipate, diisopropyl sebacate, lauryl lactate, myristyl lactate, and cetyl lactate.

7. Alkenyl esters of fatty acids having 10 to 20 carbon atoms. Examples thereof include oleyl myristate, oleyl stearate, and oleyl oleate.

8. Fatty acids having 9 to 22 carbon atoms. Suitable examples include pelargonic, lauric, myristic, palmitic, stearic, isostearic, hydroxystearic, oleic, linoleic, ricinoleic, arachidic, behenic, and erucic acids.

9. Fatty alcohols having 10 to 22 carbon atoms. Lauryl, myristyl, cetyl, hexadecyl, stearyl, isostearyl, hydroxystearyl, oleyl, ricinoleyl, behenyl, erucyl, and 2-octyl dodecyl alcohols are examples of satisfactory fatty alcohols.

10. Fatty alcohol ethers. Ethoxylated fatty alcohols of 10 to 20 carbon atoms include the lauryl, cetyl, stearyl, isostearyl, oleyl, and cholesterol alcohols having attached thereto from 1 to 50 ethylene oxide groups or 1 to 50 propylene oxide groups, or a mixture thereof.

11. Ether esters such as fatty acid esters of ethoxylated fatty alcohols.

12. Lanolin and derivatives. Lanolin, lanolin oil, lanolin wax, lanolin alcohols, lanolin fatty acids, isopropyl lanolate, ethoxylated lanolin, ethoxylated lanolin alcohols, ethoxylated cholesterol, propoxylated lanolin alcohols, acetylated lanolin, acetylated lanolin alcohols, lanolin alcohols linoleate, lanolin alcohols ricinoleate, acetate of lanolin alcohols ricinoleate, acetate of ethoxylated alcohols-esters, hydrogenolysis of lanolin, ethoxylated hydrogenated lanolin, ethoxylated sorbitol lanolin, and liquid and semisolid lanolin absorption bases are illustrative of emollients derived from lanolin.

13. Polyhydric alcohols and polyether derivatives. Propylene glycol, dipropylene glycol, polypropylene

glycol (M.W. 2000—4000), polyoxyethylene polyoxypropylene glycols, polyoxypropylene polyoxyethylene glycols, glycerol, ethoxylated glycerol, propoxylated glycerol, sorbitol, ethoxylated sorbitol, hydroxypropyl sorbitol, polyethylene glycol (M.W. 200—6000), methoxy polyethylene glycols 350, 550, 750, 2000, 5000, poly[ethylene oxide] homopolymers (M.W. 100,000—5,000,000), polyalkylene glycols and derivatives, 5 hexylene glycol (2-methyl-2,4-pentanediol), 1,3-butylene glycol, 1,2,6-hexanetriol, ethohexadiol USP (2-ethyl-1,3-hexanediol), C₁₅—C₁₈ vicinal glycol, and polyoxypropylene derivatives of trimethylolpropane are examples thereof.

14. Polyhydric alcohol esters. Ethylene glycol mono- and di-fatty acid esters, diethylene glycol mono- and di-fatty acid esters, polyethylene glycol (M.W.200—6000) mono- and di-fatty acid esters, propylene 10 glycol mono- and di-fatty acid esters, polypropylene glycol 2000 monooleate, polypropylene glycol 2000 monostearate, ethoxylated propylene glycol monostearate, glyceryl mono- and di-fatty acid esters, polyglycerol poly-fatty acid esters, ethoxylated glyceryl monostearate, 1,3-butylene glycol monostearate, 1,3-butylene glycol distearate, polyoxyethylene polyol fatty acid ester, sorbitan fatty acid esters, and polyoxyethylene sorbitan fatty acid esters are satisfactory polyhydric alcohol esters.

15 15. Wax esters such as beeswax, spermaceti, myristyl myristate, stearyl stearate.

16. Beeswax derivatives, e.g. polyoxyethylene sorbitol beeswax. These are reaction products of beeswax with ethoxylated sorbitol of varying ethylene oxide content, forming a mixture of ether-esters.

17. Vegetable waxes including carnauba and candelilla waxes.

18. Phospholipids such as lecithin and derivatives.

20 19. Sterols. Cholesterol, cholesterol fatty acid esters are examples thereof.

20. Amides such as fatty acid amides, ethoxylated fatty acid amides, solid fatty acid alkanolamides.

The lotions further comprise from 1% to 10%, preferably from 2% to 5%, of an emulsifier. The emulsifiers can be nonionic, anionic or cationic. Examples of satisfactory nonionic emulsifiers include fatty 25 alcohols having 10 to 20 carbon atoms, fatty alcohols having 10 to 20 carbon atoms condensed with 2 to 20 moles of ethylene oxide or propylene oxide, alkyl phenols with 6 to 12 carbon atoms in the alkyl chain condensed with 2 to 20 moles of ethylene oxide, mono- and di-fatty acid esters of ethylene glycol wherein the fatty acid moiety contains from 10 to 20 carbon atoms, fatty acid monoglycerides wherein the fatty acid moiety contains from 10 to 20 carbon atoms, diethylene glycol, polyethylene glycols of molecular weight 200 to 6000, propylene glycols of molecular weight 200 to 3000, glycerol, sorbitol, sorbitan, polyoxyethylene sorbitol, polyoxyethylene sorbitan, and hydrophilic wax esters. Suitable anionic emulsifiers 30 include the fatty acid soaps, e.g. sodium, potassium and triethanolamine soaps, wherein the fatty acid moiety contains from 10 to 20 carbon atoms. Other suitable anionic emulsifiers include the alkali metal, ammonium or substituted ammonium alkyl sulfates, alkyl arylsulfonates, and alkyl ethoxy ether sulfonates having 10 to 30 carbon atoms in the alkyl moiety. The alkyl ethoxy ether sulfonates contain from 1 to 50 35 ethylene oxide units. Satisfactory cationic emulsifiers are the quaternary ammonium, morpholinium and pyridinium compounds. Certain of the emollients described in preceding paragraphs also have emulsifying properties. When a lotion is formulated containing such an emollient, an additional emulsifier is not needed, though it can be included in the composition.

The balance of the lotion is water or a C₂ or C₃ alcohol, or a mixture of water and the alcohol. The 40 lotions are formulated by simply admixing all of the components together. Preferably the sulfonamide is dissolved in the mixture. Optional components such as common additives can be included. One common additive is a thickening agent at a level from 1% to 10% of the composition. Examples of suitable thickening agents include: cross-linked carboxypolymethylene polymers, ethyl cellulose, polyethylene glycols, gum tragacanth, gum kharaya, xanthan gums and bentonite.

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2. Creams

Compositions of this invention also can be formulated in a cream form. The creams comprise an effective amount of the sulfonamide; from 5% to 50%, preferably from 10% to 25%, of an emollient; the balance being water. The emollients above described can also be used in the cream compositions. 50 Optionally the cream form contains a suitable emulsifier, as previously described. When an emulsifier is included, it is in the composition at a level from 3% to 50%, preferably from 5% to 20%.

3. Solutions

The compositions of this invention can be also formulated in a solution form. The solution form 55 comprises an effective amount of the sulfonamide; the balance being a suitable organic solvent. Suitable organic materials useful as the solvent or a part of a solvent system are as follows: propylene glycol, polyethylene glycol (M.W. 200—600), polypropylene glycol (M.W. 425—2025), glycerine, sorbitol esters, 1,2,6-hexanetriol, ethanol, isopropanol, diethyl tartrate, butanediol, and mixtures thereof. Such solvent systems can also contain water.

60 These compositions in the solution form can be applied to the skin as is, or else can be formulated into an aerosol and applied to the skin as a spray-on. The aerosol compositions further comprise from 25% to 80%, preferably from 30% to 50%, of a suitable propellant. Examples of such propellants are the chlorinated, fluorinated and chlorofluorinated lower molecular weight hydrocarbons. Nitrous oxide, carbon dioxide, butane, and propane are also used as propellant gases. These propellants are used at a 65 level sufficient to expel the contents of the container.

4. Gels

Compositions herein can be formulated into a gel form by simply admixing a suitable thickening agent to the previously described solution compositions. Examples of suitable thickening agents have been previously described with respect to the lotions.

5 The gelled compositions comprise an effective amount of the sulfonamide; from 5% to 75%, preferably from 10% to 50%, of an organic solvent as previously described; from 0.5% to 20%, preferably from 1% to 10% of the thickening agent; the balance being water.

5. Solids

10 The compositions of this invention can also be formulated into a solid form. Such forms have use as a stick-type composition intended for application to the lips or other parts of the body. Such compositions comprise an effective amount of the sulfonamide and from 50% to 98%, preferably from 60% to 90%, of the previously described emollients. This composition can further comprise from 1% to 20%, preferably from 5% to 15%, of a suitable thickening agent, and optionally emulsifiers and water. Thickening agents
15 previously described with respect to the gelled compositions are suitable herein.

Additives commonly found in topical compositions such as preservatives, e.g., methyl and ethyl-paraben, dyes and perfume can be included in any of the previously described compositions.

D. Pharmaceutical Compositions and Dosage Forms for Systemic Administration

20 The sulfonamides of the present invention are also useful when used systemically, for example by parenteral administration. The dosage of the sulfonamide which is both safe and effective to provide analgesic or anti-irritant activity will vary with the particular condition being treated, the severity of the condition, the duration of treatment, the specific sulfonamide employed and its usage concentration, and like factors within the specific knowledge and expertise of the patient or the attending physician and
25 commensurate with a reasonable benefit/risk ratio associated with the use of any drug compound. The systemic dosages and dosage ranges given herein are based on delivery of the sulfonamide to a 70kg human and can be adjusted to provide equivalent dosages for patients of different body weights.

For mammals, especially humans, individual doses of from 0.1 mg to over 100 mg with total dosages of from 0.5 mg to 500 mg are acceptable. Individual doses of from 0.5 mg to 50 mg with total dosages of
30 from 1 mg to 100 mg are preferred. Individual doses of from 5 mg to 25 mg with total dosages of from 10 mg to 50 mg are especially preferred. While dosages higher than the foregoing are effective, toxicity and side effects will present problems in some individuals.

The sulfonamides can be administered parenterally in combination with a pharmaceutically acceptable carrier such as corn oil, Cremophor EL or sterile, pyrogen-free water and a water-miscible solvent (e.g.,
35 ethyl alcohol) at a practical amount of the sulfonamide per dose. Parenteral administration can be by subcutaneous, intradermal, intramuscular, intraarticular, or intravenous injection. The dosage by these modes of administration is usually in the range of from about 10 mg to about 500 mg per day.

As used herein the term "pharmaceutically acceptable carrier" denotes a solid or liquid filler, diluent, or encapsulating substance. Some examples of substances which can serve as pharmaceutical carriers for
40 the sulfonamides include: sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives, such as sodium carboxymethylcellulose, ethyl cellulose, cellulose acetate, powdered tragacanth; malt; gelatin; talc, stearic acid magnesium stearate; calcium sulfate; vegetable oils, such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil and oil of theobroma; polyols such as propylene glycol, glycerin, sorbitol, mannitol, and polyethylene glycol; sugar;
45 alginic acid; pyrogen-free water; isotonic saline; phosphate buffer solutions; cocoa butter (suppository base), emulsifiers, such as the Tweens[®] as well as other non-toxic compatible substances typically used on pharmaceutical formulations. Wetting agents and lubricants such as sodium lauryl sulfate, as well as coloring agents, flavoring agents and preservatives, can also be present.

The pharmaceutical carrier employed in conjunction with the sulfonamide is used at a concentration
50 sufficient to provide a practical size to dosage relationship. Preferably, the pharmaceutical carrier comprises at least about 98% by weight of the total composition.

E. Methods for Providing Analgesia and Anti-irritancy

55 The present invention encompasses methods for providing analgesia or anti-irritancy in humans or lower animals in need thereof by administering a safe and effective amount, usually from about 10 mg to about 500 mg per patient per day, of the sulfonamide, usually as a composition with a pharmaceutically acceptable carrier. The sulfonamides and compositions containing same can be administered by topical application or systemic administration. The sulfonamides and compositions containing same can be used to treat pain and to provide an analgesic effect in various disorders at the deeper structures, muscles,
60 tendons, bursa and joints associated with disease and trauma, and in various other conditions in which compounds such as aspirin and morphine have heretofore been used to alleviate pain and discomfort.

A "stairstep" dose pattern of sequentially increasing doses is useful for intraperitoneal administration in overcoming temporary side effects and in administering larger doses of the sulfonamides of this invention. While not intending to be limited by theory, experimental results suggest that it is the final,
65 maximal dose, and not the total dose administered, which is most important to efficacy at high dosage

levels. Thus, the initial dose should be selected to provide minimal side effects, and subsequent doses should be increased until the desired level of activity is obtained while still minimizing side effects. In general, an initial dose of 2—10 mg/kg can be conveniently used, followed by doubling of each subsequent dose until the desired level is reached. The doses are preferably separated by a period of at least two hours.

F. Depilatory Compositions Having Reduced Dermal Irritation and Methods for Reducing or Preventing Irritation Caused by Depilatory Agents

The present invention also encompasses depilatory compositions having reduced dermal irritation, which comprise: a) a depilatory amount (e.g. at least about 2%) of a thioglycolate depilatory agent; and b) the sulfonamide in an amount effective to reduce the dermal irritation caused by the thioglycolate depilatory agent. The depilatory compositions can be formulated using the pharmaceutically acceptable carriers previously described for topical compositions.

The present invention further encompasses a method for preventing or reducing the dermal irritation caused by a thioglycolate depilatory agent, which comprises the step of applying to at least a portion of a depilated area the sulfonamide (or composition containing same) in an amount effective to prevent or reduce the irritation caused by treatment of the depilated area with the thioglycolate depilatory agent.

By "thioglycolate depilatory agent" is meant thioglycolic acid, its alkali metal, alkaline earth metal, and ammonium salt(s), or mixtures of the acid and its salt(s).

By "an amount effective to prevent or reduce irritation" is meant an amount of the sulfonamide (or composition containing same) effective to reduce or prevent the irritation caused by treatment of the depilated area with the thioglycolate depilatory agent at a reasonable benefit/risk ratio. The amount of the sulfonamide used will vary with the severity of the irritation, the duration of the treatment, the specific formulation employed, the concentration of the sulfonamide therein, and like factors.

By "depilated area" is meant that area which is, or is about to be, depilated by treatment with a thioglycolate depilatory agent.

By the term "applying" with regard to preventing or reducing depilatory irritation is meant the direct laying on or spreading of the sulfonamide (including compositions containing same) on skin tissue which is, or is about to be depilated. The sulfonamide can be applied before and/or after treatment of the depilated area with the thioglycolate depilatory agent to prevent or reduce irritation caused thereby.

Application of the sulfonamide to the depilated area after treatment with the depilatory agent is preferred, especially when lower concentrations of the sulfonamide are used. The number of applications needed to provide effective irritation prevention or reduction can depend upon the concentration of the sulfonamide used, and when the sulfonamide is applied in relation to the treatment with the depilatory agent.

Application of the sulfonamide soon after depilation, e.g. within about 6 to about 12 hours, provides effective irritation prevention or reduction, especially in conjunction with additional applications on subsequent days. Multiple applications (2 or more sequential, time spaced applications) soon after depilation are particularly effective. The length of time during which the sulfonamide is left on the depilated area can also determine its effectiveness. An application duration of at least about 1 hour, preferably from about 1 to about 2 hours, should provide effective irritation prevention or reduction.

Specific Embodiments of Compositions Containing N-(3-Methoxy-4-Hydroxybenzyl) Sulfonamides

The following examples illustrate compositions within the scope of the present invention, but are not limiting thereof.

Embodiment I

Lotion

Isopropyl myristate	8%
Corn oil	5%
Propylene glycol	5%
Triethanolamine oleate	5%
Xanthan gum	0.5%
N-(3-methoxy-4-hydroxybenzyl)-dodecylsulfonamide	0.5%
Water	Balance

0 068 591**Embodiment II****Cream**

5	Isopropyl myristate	5%
	Sorbitol	5%
	Propylene glycol	10%
10	Triethanolamine stearate	17%
	N-(3-methoxy-4-hydroxybenzyl) dodecylsulfonamide	1%
15	Water	Balance

Embodiment III**Gel**

20	Oleyl alcohol	1%
	Propylene glycol	20%
25	Triethanolamine	0.5%
	Ethanol	57%
	Carbomer 940	0.5%
30	N-(3-methoxy-4-hydroxybenzyl) <i>cis</i> -12-docosenylsulfonamide	0.5%
	Water	Balance

Embodiment IV**Solution**

	Propylene glycol	10%
40	Polyethylene glycol 400	2%
	Tween 80 ^R	1%
45	Ethanol	50%
	N-(3-methoxy-4-hydroxybenzyl) hexenylsulfonamide	1%
	Water	Balance

Embodiment V**Ointment**

55	Oleyl alcohol	30%
	Cetyl alcohol	40%
	Propylene glycol	28%
60	N-(3-methoxy-4-hydroxybenzyl) 3-phenylpropylsulfonamide	2%

65

Effectiveness of N-(3-Methoxy-4-Hydroxybenzyl) Sulfonamides in Producing Analgesia and in Reducing or Preventing Depilatory Irritation

A. Analgesia

1. Mouse Hot Plate Tests

The Mouse Hot Plate (MHP) model system is designed to detect and evaluate agents which elevate the threshold for the perception of pain. Classically, this method has been utilized primarily to evaluate narcotic type analgesic agents such as morphine. Unless administered in toxic quantities, nonsteroidal anti-inflammatory agents such as aspirin or acetaminophen exhibit little or no activity in this system.

Male CF-1 mice were used. Animals were divided into groups of 8 to 12 and then tested on the "hot plate" to determine their predrug response time which was 4.9 seconds (average). Each animal was then treated with either a test composition (0.5% to 2% of the particular N-(3-methoxy-4-hydroxybenzyl) sulfonamide in an isotonic saline solution containing ethyl alcohol and Tween 80) or a control composition (same as test composition but without the sulfonamide). Treatment was by injection prior to test initiation.

2. Procedure

The mice were placed on a 55°C heated surface and their responses were observed. The endpoint is either a rapid fanning or licking of a paw. To prevent physical injury, the animals were not allowed to remain in contact with the heated surface for more than 60 seconds. The exposure time required to elicit the endpoint response is a measure of the pain threshold. The difference in time required to elicit the endpoint response before and after treatment provides a measure of analgesia. The increase in time required to elicit the endpoint response in treated animals versus control composition is a second measure.

3. Results

The results from the MHP testing of the N-(3-methoxy-4-hydroxybenzyl) sulfonamides were as follows:

TABLE I

Compound	Method**	Dosage*** (mg/kg)	Post-Drug Response (sec)
Aspirin*	O	360	6.0
Acetaminophen*	O	450	5.3
Morphine Sulfate*	IP	13	13.1
Morphine Sulfate*	IP	25	17.4
Control	SC or IP	—	4.9—5.0
Heptyl	SC	0.68 mM/kg	6.8
Heptyl	IP	150	16.2****
Heptyl	SC	108	7.0
Heptyl	IP	108	17.3
Octyl	SC	150	9.2
Octyl	SC	4,8,15,25	7.5
Octyl	SC	112	8.2
Octyl	IP	112	11.4

* Commercial Analgesics

** O — oral; SC subcutaneous; IP — intraperitoneal

*** Multiple doses were 2 hours apart

**** 70% of animals dead

***** IP dose was 24 hrs. after SC dose

The data in Table I shows that both N-(3-methoxy-4-hydroxy-benzyl) heptylsulfonamide and octyl-sulfonamide have significant analgesic activity relative to the control composition and the commercial analgesics.

5 B. Preventing or Reducing Depilatory Irritation

Groups of 8 male Sprague-Dawley rats weighing 90—115 grams were used for testing the effectiveness of the N-(3-methoxy-4-hydroxybenzyl) sulfonamides of the present invention in preventing or reducing depilatory irritation. The animals were clipped and depilated with Nair[®], a commercially available thioglycolate depilatory. The test compositions (2% of the N-(3-methoxy-4-hydroxybenzyl) sulfonamide in an isotonic saline solution containing 48% ethyl alcohol, 4% Tween 80) or a control composition (same as test composition but without the sulfonamide) were applied to one quadrant (Treated Area) of the depilated area once, 2 hours after depilation on first day; four times, 2 hours apart on second day; and three times, 2 hours apart on third day for a total of eight applications. The duration of each application was 2 hours. The remaining three quadrants of the depilated area were left untreated (Untreated Area). Oral ingestion was prevented by the use of "Elizabethan" collars. On the fourth day, the animals were depilated a second time and evaluated for irritation four hours later.

Irritation scores for each animal were determined by visual inspection using the following subjective evaluation scale:

20	Score	Description of Irritation
	0	No irritation
	0.5	No scab formation, faint white scale
25	1.0	Scab formation (pale orange/orange) over less than 10% of area
	2.0	Mild to moderate intensity scab formation (pale orange) over 10—33% of area
30	3.0	Mild to moderate intensity scab formation (pale orange) over 33—75% of area
	3.5	Moderate intensity scab formation (pale orange, occasional deep orange/red) over 75—90% of area
35	4.0	Moderate to severe intensity scab formation (deep orange, occasional pale orange) over 90—100% of area
	5.0	Severe intensity scab formation (deep orange/red) over 100% of area

40 The irritation scores were totaled for each of the 8-animal groups, the maximum cumulative score being 40. A cumulative score of less than 8 indicated a minimal level of irritation; a score of 8—24 indicated a higher, but acceptable level of irritation; a score of above 24 indicated an unacceptable level of irritation. The results from this testing of the N-(3-methoxy-4-hydroxybenzyl) sulfonamides were as follows:

45 TABLE II

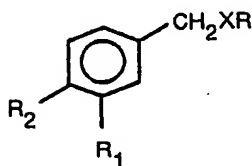
50	Composition	Cumulative Score	
		Treated Area	Untreated Area
	Control	34	27.5
	Octyl	11	2

55 The data in Table II shows that N-(3-methoxy-4-hydroxybenzyl) octylsulfonamide was effective in preventing or reducing depilatory irritation.

Claims

1. A compound characterized in that it has the formula:

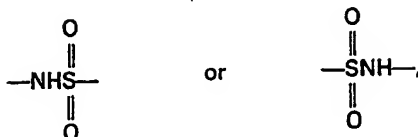
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wherein X is

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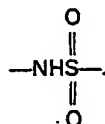
wherein R is C_3-C_{12} alkyl or aralkyl, branched or unbranched, unsubstituted aryl, haloaryl, or C_3-C_{22} alkenyl, branched or unbranched, wherein R_1 is H, OH or OCH_3 , and wherein R_2 is H or OH, at least one of R_1 and R_2 being OH or OCH_3 ; and pharmaceutically acceptable salts thereof.

2. The compound of Claim 1 characterized in that it is the sodium, potassium, calcium, magnesium, or ammonium salt.

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3. The compound or salt of Claim 1 or 2 characterized in that X is

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4. The compound or salt of any of Claims 1—3 characterized in that R_1 is OCH_3 and R_2 is OH.

5. The compound or salt of any of Claims 1—4 characterized in that R is C_6-C_{12} alkyl or aralkyl, or C_6-C_{22} alkenyl.

6. The compound or salt of any of Claims 1—5 characterized in that R is n-heptyl or n-octyl.

7. A pharmaceutical composition in unit dosage form having analgesic activity characterized in that it comprises a safe and effective amount of the compound or salt of Claim 1, 2, 3, 4, 5 or 6; and a pharmaceutically acceptable carrier.

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8. A depilatory composition having reduced dermal irritation, characterized in that it comprises:

a) a depilatory amount of a thioglycolate depilatory agent, and

b) a compound or salt of any of Claims 1—6 in an amount effective to prevent or reduce the dermal irritation of the thioglycolate depilatory agent.

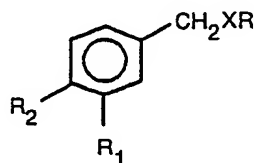
9. The composition of Claim 8 characterized in that it further comprises a pharmaceutically acceptable carrier.

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Patentansprüche

1. Eine Verbindung, dadurch gekennzeichnet, daß sie die Formel

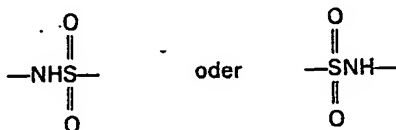
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aufweist, worin X

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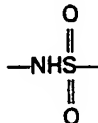
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ist, worin R eine verzweigte oder unverzweigte C₃—C₁₂-Alkyl- oder -Aralkylgruppe, nichtsubstituierte Arylgruppe, Halogenarylgruppe oder eine verzweigte oder unverzweigte C₃—C₂₂-Alkenylgruppe ist, worin R₁ H, OH oder OCH₃ ist, und worin R₂ H oder OH ist, wobei mindestens einer der Reste R₁ und R₂ OH oder OCH₃ ist; und deren pharmazeutisch annehmbare Salze.

- 5 2. Die Verbindung gemäß Anspruch 1, dadurch gekennzeichnet, daß sie das Natrium-, Kalium-, Calcium-, Magnesium- oder Ammoniumsalz ist.

3. Die Verbindung oder das Salz gemäß Anspruch 1 oder 2, dadurch gekennzeichnet, daß X

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ist.

- 15 4. Die Verbindung oder das Salz nach einem der Ansprüche 1 bis 3, dadurch gekennzeichnet, daß R₁ OCH₃ ist und R₂ OH ist.

5. Die Verbindung oder das Salz nach einem der Ansprüche 1 bis 4, dadurch gekennzeichnet, daß R eine C₆—C₁₂-Alkyl- oder -Aralkylgruppe oder eine C₆—C₂₂-Alkenylgruppe ist.

6. Die Verbindung oder das Salz nach einem der Ansprüche 1 bis 5, dadurch gekennzeichnet, daß R die n-Heptylgruppe oder die n-Octylgruppe ist.

20 7. Eine pharmazeutische Zusammensetzung in Einheitsdosierungsform mit schmerzlindernder Wirksamkeit, dadurch gekennzeichnet, daß sie eine sichere und wirksame Menge der Verbindung oder des Salzes nach Anspruch 1, 2, 3, 4, 5 oder 6 und einen pharmazeutisch annehmbaren Träger enthält.

8. Enthaarungsmittel mit verringerter Hautreizung, dadurch gekennzeichnet, daß es enthält:

- 25 a) eine enthaarende Menge eines Thioglycolat-enthaarungsmittels und
b) eine Verbindung oder ein Salz nach einem der Ansprüche 1 bis 6 in einer Menge, die wirksam ist, um die Hautreizung des Thioglycolat-enthaarungsmittels zu verhindern oder zu verringern.

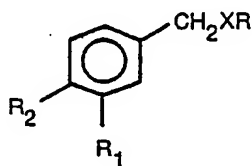
9. Mittel gemäß Anspruch 8, dadurch gekennzeichnet, daß es weiterhin einen pharmazeutisch annehmbaren Träger enthält.

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Revendications

- 35 1. Composé caractérisé en ce qu'il a pour formule:

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45 dans laquelle X représente



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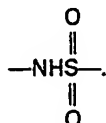
où R représente un groupe en C₃ à C₁₂, ramifié ou non ramifié, alkyle ou aralkyle, aryle non substitué, halogénoaryle, ou alkényle en C₃ à C₂₂, ramifié ou non ramifié; R₁ représente H, OH ou OCH₃, et R₂ représente H ou OH, au moins l'un des symboles R₁ et R₂ représentant OH ou OCH₃, et ses sels pharmaceutiquement acceptables.

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2. Composé selon la revendication 1, caractérisé en ce qu'il est le sel de sodium, de potassium, de calcium, de magnésium ou d'ammonium.

3. Composé ou sel selon la revendication 1 ou 2, caractérisé en ce que X représente

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4. Composé ou sel selon l'une quelconque des revendications 1 à 3, caractérisé en ce que R₁ représente OCH₃ et R₂ représente OH.

5. Composé ou sel selon l'une quelconque des revendications 1 à 4, caractérisé en ce que R représente un groupe alkyle ou aralkyle en C₆ à C₁₂ ou bien un groupe alkényle en C₆ à C₂₂.

5 6. Composé ou sel selon l'une quelconque des revendications 1 à 5, caractérisé en ce que R représente un groupe n-heptyle ou n-octyle.

7. Composition pharmaceutique, sous forme de dose unitaire ayant une activité analgésique, caractérisée en ce qu'elle comprend une quantité non toxique et efficace d'un composé ou d'un sel selon la revendication 1, 2, 3, 4, 5, ou 6; et un véhicule pharmaceutiquement acceptable.

10 8. Composition dépilatoire causant moins d'irritation dermique caractérisée en ce qu'elle comprend:

a) une quantité dépilatoire, d'un agent dépilatoire de type thioglycolate, et

b) un composé ou sel selon l'une quelconque des revendications 1 à 6, en une quantité suffisante pour prévenir ou diminuer l'irritation dermique due à l'agent dépilatoire de type thioglycolate.

15 9. Composition selon la revendication 8, caractérisée en ce qu'elle comprend en outre un véhicule pharmaceutiquement acceptable.

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